

# NEW DRUG EVALUATION

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## METHYLNALTREXONE

Methylnaltrexone is the first peripherally-acting opioid receptor antagonist to be licensed for the treatment of opioid-induced constipation (OIC) in adults with advanced illness receiving palliative care, when response to usual laxative therapy has been inadequate. When added to laxative therapy, it significantly improved the rate of bowel movements and appeared to be well tolerated; the most common adverse effects being abdominal pain and flatulence. In trials, methylnaltrexone alleviated OIC without compromising analgesia. Methylnaltrexone is a novel treatment option for laxative-resistant OIC, but prescribing should be restricted to palliative care specialists for exceptional use when maximal conventional laxative therapy is ineffective.

### What is it?

Methylnaltrexone (Relistor<sup>®</sup>▼, Wyeth Pharmaceuticals) is a peripherally-acting mu-opioid receptor antagonist indicated for the treatment of opioid-induced constipation (OIC) in adults with advanced illness, who are receiving palliative care, when response to usual laxative therapy has been inadequate.<sup>1</sup> Methylnaltrexone should be added to patients existing laxative therapy and administered subcutaneously (SC) at a dose of either 8 mg (for patients weighing 38 - 61 kg), 12 mg (for patients weighing 62 - 114 kg) or 0.15 mg/kg for patients outside these ranges.<sup>1</sup> The usual administration schedule is a single dose every other day, adjusted according to clinical need.<sup>1</sup> In addition, two consecutive doses may be given 24 hours apart, but only when there has been no laxation response to the dose on the preceding day.<sup>1</sup> As methylnaltrexone has restricted ability to cross the blood-brain barrier, it has the potential to alleviate the undesired peripheral adverse effects of opioids without compromising central analgesia.<sup>1</sup>

### How effective is it?

The efficacy and safety of methylnaltrexone in the treatment of OIC have been evaluated in two multicentre, randomised, double-blind, placebo-controlled phase III trials involving adults with advanced illness (life expectancy of 1 - 6 months) who were receiving palliative care.<sup>2-4</sup> The majority of patients had incurable cancer, but other diagnoses included cardiovascular disease, chronic obstructive pulmonary disease or emphysema and Alzheimer's disease or dementia. Trial inclusion criteria included: patients taking stable doses of opioids and laxatives for  $\geq 3$  days<sup>2-5</sup> and OIC (defined as no bowel movements for  $> 48$  hours<sup>2,3</sup> or  $< 3$  in the preceding week<sup>4</sup>).

Throughout all study periods, patients maintained their usual laxative regimen. The laxative regimens were broadly similar, on average patients were using two different types of laxative, although it is unclear whether therapy had been optimised. The primary endpoints were rescue-free laxation, defined as a bowel movement without the use of a rescue laxative such as an enema,<sup>4</sup> within four hours of the first dose of methylnaltrexone<sup>2-4</sup> and rescue-free laxation within four hours of two or more of the first four doses.<sup>4</sup> Secondary endpoints included time to laxation, pain scores, opioid withdrawal symptoms and adverse events.

The first study is fully published and compared methylnaltrexone 0.15 mg/kg (n = 62) with placebo (n = 71), administered every other day for two weeks.<sup>4</sup> In the second week, the dose was increased to 0.3 mg/kg if the patient had fewer than three laxations by day eight. Methylnaltrexone improved the laxation rate within four hours of the first dose compared with placebo [48% vs. 15% (p < 0.001)]<sup>4</sup>. The percentage of remaining patients who responded outside this four hour period was not made clear. Of the patients who did respond within four hours of the first dose, half responded within 30 minutes.<sup>4</sup> The study also showed that 52% of all patients taking methylnaltrexone had rescue-free laxation within four hours of  $\geq$  two of the first four doses, compared with 8% in the placebo group (p < 0.001).<sup>4</sup>

The second study, available as an abstract and in the EMEA assessment report, compared single SC doses of methylnaltrexone 0.15 mg/kg (n = 47) or 0.30 mg/kg (n = 55), with placebo (n = 52).<sup>2,3,5</sup> Methylnaltrexone significantly improved the laxation rate within four hours of dosing [62% for 0.15 mg/kg and 58% for 0.30 mg/kg vs. 14% for placebo (p < 0.0001 for each dose vs. placebo)].<sup>5</sup> The median time to laxation was shorter in the group administered methylnaltrexone [70 minutes and 45 minutes

for the 0.15 mg/kg and 0.30 mg/kg groups respectively, compared with placebo (> 24 hours) (p < 0.0001 for each dose vs. placebo)].<sup>2</sup>

Following these studies, it remains unclear whether the addition of methylnaltrexone to current laxative therapy is of more benefit than optimising existing laxative therapy to achieve maximal efficacy. The second study is limited as administration of a single dose may not replicate clinical practice.

### How safe is it?

In phase III trials, SC methylnaltrexone was well tolerated in patients with OIC and an advanced illness. The most common adverse effects reported, for all doses of methylnaltrexone, are shown below.<sup>5</sup>

Adverse reaction	Methylnaltrexone (n = 165)	Placebo (n = 123)
Abdominal pain	28.5%	9.8%
Flatulence	13.3%	5.7%
Nausea	11.5%	4.9%
Dizziness	7.3%	2.4%
Diarrhoea	5.5%	2.4%

Investigators deemed that all serious adverse events were not related or unlikely to be related to the study drug. The incidence of life-threatening adverse events was similar in both groups and was judged to be related to underlying disease progression.<sup>4</sup> There was no evidence of systemic opioid withdrawal, or significant changes in pain scores throughout the studies.<sup>2,4</sup>

All suspected adverse reactions to black triangle drugs▼, such as methylnaltrexone should be reported to the MHRA via the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

### What other options are there?

Clinical Knowledge Summary guidelines recommend combining softening and stimulant laxatives for the prophylaxis and treatment of constipation in palliative care, including OIC.<sup>6</sup> Faecal impaction and other contributory

factors (e.g. diet / lifestyle) should be addressed first, where appropriate. If initial laxative therapy is unsuccessful and intestinal obstruction is ruled out, then a macrogol or prokinetic drug may be added.<sup>6</sup> However, currently available laxatives do not target the underlying cause of OIC. Whilst non-selective opioid receptor antagonists such as naloxone have been used off-licence to treat OIC, their use is usually inappropriate as they readily cross the blood-brain barrier, and thus have potential to reverse analgesia.<sup>7,8</sup>

### When should it be used?

Methylnaltrexone should only be considered for use by palliative care specialists, when constipation is related to opioid use and optimal / maximised laxative combinations, or rectal measures (where appropriate), have not been effective. The patient's laxative regimen must be continued whilst taking methylnaltrexone.

Methylnaltrexone is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction or acute surgical abdomen.<sup>1</sup> It is not recommended in patients with end-stage renal impairment requiring dialysis, however patients with severe renal impairment should receive a reduced dose.<sup>1</sup>

Methylnaltrexone is also not recommended for use in patients with severe hepatic impairment; however those with mild to moderate impairment do not require dose reduction.<sup>1</sup> It should be used with caution in patients with colostomy, peritoneal catheter, active diverticular disease or faecal impaction.<sup>1</sup> Methylnaltrexone has not been studied in clinical trials for longer than four months.

### How much does it cost?

The cost of methylnaltrexone is £21.05 per 0.6 ml vial (containing 12 mg of methylnaltrexone).<sup>9</sup> The usual administration schedule is one single dose every other day,<sup>1</sup> therefore would cost £294.70 for 28 days treatment (14 doses). Approximately 80% of people with cancer will require laxatives and about 6.5 per 100,000 people have laxative-resistant constipation.<sup>10</sup>

Laxative cost comparison charts are available at [http://www.nyrdtc.nhs.uk/Services/presc\\_supp/presc\\_supp.html](http://www.nyrdtc.nhs.uk/Services/presc_supp/presc_supp.html)

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KEY RCT - randomised controlled trial, G - guideline, R - Review, Abs - abstract.

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